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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/600,493	WANDS ET AL
	Examiner	Art Unit
	Christopher Drabik	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. 35 U.S.C. § 133.
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,6-8,10-28,32 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,6-8,10-28,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4)☐ Interview Summary (PTO-413) Paper No(s). _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

Applicants amendment and response to the Office Action mailed on December 8, 2001 as paper No. 4. has been received and filed on May 16, 2001 as paper No.6. Claims 1, 5, 9 and 29-31 have been cancelled. Claims 2-4, 6-8, 10-28 32 and 33 are currently pending. Applicants amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Applicants arguments are addressed below on a per section basis. The text of those sections of Title 35. U.S. Code not included in this Action can be found in a prior Office Action.

Response to Arguments

Claim Rejections - 35 USC § 112

Claims 10-28, 32 and 33 stand rejected for reasons of record. Applicants assert that they have sufficiently provided an enabling disclosure for the prophylactic immunization of humans against HCV infection or therapeutic immunization against acquired infection. Applicants arguments have been considered but are non-persuasive for the following reasons.

Applicants point out that the appropriate criteria for enablement is embodied in the 1988 Federal Circuit decision In re Wands. The examiner has considered the factors delineated in Wands reviewing the instant application and the standing

enablemement rejections are firmly based in the evaluation of the relavant Wands factors.

Regarding the breadth of the subject matter and the nature of the invention. The disclosure and claims clearly point out that the use of the claimed invention is for prophylactic or therapeutic use. Applicants argue in their response to the enablement rejections set forth by the examiner that the object of the claimed invention is to merely elicit an immune response. And, further, that any immune response would be beneficial to a patient in need. However, applicants disclose that the invention is drawn to more than just an immune response. In the Summary of the Invention, At page 6, lines 17-19. "The individual is administered a DNA vaccine in an *amount effective to induce a protective immune response* against hepatitis C infection." At page 6 lines 26-27. " The individual is administered an *amount effective to induce a therapeutic immune response*." Examiner maintains the argument that there has been no demonstration of a prophylactic or therapeutic immunization based on the course of an HCV infection, but rather applicants conclusions are based on the effects of a mouse model in which the course of an HCV infection cannot be modeled.

In considering the state of the art regarding the fields understanding of the course of HCV infection and the immune response to HCV, applicants correctly point out that " The cellular immune events involved in liver damage and viral clearance during HCV infection have only partially been defined." (page 2, lines 30 –31 of the instant application) And further: "...it is unknown if the non-structural proteins NS3, NS4 and NS5 are sufficiently immunogenic to generate a broad based and vigorous CTL-

response in vivo." The examiner points out that Applicants have not provided sufficient evidence that a CTL immune response capable of preventing infection has been demonstrated or that any immune response capable of effecting the course of the disease has been demonstrated. A point not relied upon by the examiner in the arguments made against enablement is correctly delineated by Applicants: "Development of a vaccine strategy for HCV is complicated not only by the significant heterogeneity among HCV isolates, but also by the mixture of heterogenous genomes within an isolate. " The heterogeneity of HCV genomes does not only include structural proteins, but also encompasses the non-structural proteins as well. For example, it has been demonstrated that the RdRp of HCV has regions responsive to interferon which become mutated upon drug selection pressure. It is unclear whether the applicants have provided sufficient enabling evidence to indicate that the DNA vaccines comprising any epitope of HCV NS3 , NS4 or NS5 would elicit a significant immune response in humans The scope of the claims are directed to the NS3, NS4 and NS5 proteins and any fragment thereof. In regard to the state of the prior art of DNA vaccination in general and HCV DNA vaccination in particular. The examiner directs applicants to the prior Office Action.

Applicants cite In re Marzocchi 169 USPQ 367, 369-370 (C.C.P.A 1971) to indicate that that the examiner need only take into consideration whether the invention has been objectively enabled. It is incumbent upon the examiner to set forth sound reasoning and evidence to suggest that the claimed invention is not enabled. Once this has been established it becomes the burden of the applicant to present persuasive

arguments that one skilled in the art would be able to make and use the claimed invention using the application as a guide. (MPEP 2164.05). The examiner in citing Houghton in the previous Office Action has shown that there is no data in the field as to whether immune responses to HCV DNA vaccines found to generate an immune response in mice will be effective in primates. Further, Chattergoon clearly points out that while success in animals has sparked interest, there is no evidence for success in humans. The examiner reiterates the point that since mice cannot become infected with HCV, the response to an HCV vaccine in a mouse does not predict or indicate a response to the pathology of an HCV infection in an infectable host.

The arguments set forth by applicant hinge upon the assertion that an HCV DNA vaccine which elicits an immune response in mice can be used to elicit a meaningful immune response in a human. While the examiner has stated in the previous Office Action that any administration of a foreign agent such as a nucleic acid would cause an immune response, this was to make the point that *any* immune response is not necessarily specific or beneficial. Adjuvants such as mineral oil cause non-specific immune responses with little or no benefit to the patient. Vaccinations can, in fact, be detrimental to a patient. For example, the development of antibody dependent enhancement of infection (ADE) in which prior vaccination with one subtype of a virus actually increases the virulence of infection by a second subtype of the same virus. The applicants further state that whether mice are good models for HCV infection is irrelevant to analyzing whether their DNA vaccine is enabling. (page 11 approx lines 14 and 15) In fact, the applicants assertions of an immune response in mammals are

crucially dependent upon the results of the mouse experiments. Based on the novelty of DNA vaccines, without a demonstration of at least an activity in mice their would be no grounds of asserting that the vaccine could induce a response in any animal. Critical to enablement is whether this would reasonably predict success in humans for eliciting a therapeutically beneficial response. The demonstration of an immune response in a mouse to epitopes of non-structural proteins is clearly not predictive of success in humans. In a paper published by members of the inventive entity of the instant application the authors state: "...the clinical efficacy of DNA-based immunization in generating antiviral immune responses against HCV in humans remains to be established. " (Encke et al (1998) The Journal of Immunology 161:4917-4923, see sentence bridging page 4922-4923) This paper describes DNA vaccination of mice using the HCV non-structural proteins. Houghton et al, cited in the previous Office Action, point out that a critical challenge of the field of DNA vaccination is to reproduce the effects of mouse vaccination in monkeys (see first Office Action.) This disclosure indicates the field is uncertain as to whether DNA vaccinations will provide therapeutic or prohylactic immunity in monkeys or humans.

Applicants further argue at page 11, line 22 the Examiner mistakenly asserts that undue experimentation is required to induce an immune response, immunize a human or treat a human infected with HCV. Applicants demonstrate in mice that vaccination with the non-structural proteins of HCV induce a humoral and cellular immune response, however, patients infected with HCV also mount an immune response to HCV and, in most cases, this has no effect on the course of the infection.

Implicit in the assertions of the applicants is that DNA vaccination will boost a patients response to HCV such that there is some sort of benefit to the patient. However, it does not follow that the simple demonstration of a vaccination induced immune response in mice is predictive of a boost in the immunological response to HCV in humans. Even in mice, Houghton et al point out that the art has found large quantities of nucleic acids are required for apparently limited immune reactions. This points directly to the question of whether a sufficient immune response might be mounted in humans to a DNA vaccine which would be therapeutic or beneficial. Therefore, it is not apparent that teaching in the art indicates a therapeutic or prophylactic immunization of humans using HCV NS proteins is readily achievable. Considering the foregoing argument and the disclosure of Encke et al, it is obvious that further experimentation is required before DNA vaccinations using the HCV structural proteins can be performed with a reasonable likelihood of success.

On page 12 applicants assert that claims 17-28 and 32- 33 have been rejected for no substantial reason. The examiner directs applicants to the review of the prior art outlined in the previous Office Action specifically in regard to the need for further testing in the field of DNA vaccination. Based on the state of the prior art, the examiner has provided significant and substantial grounds for rejecting claims 17-28 and 32 –33. However, to briefly reiterate: Houghton states that the results of mice need to be confirmed in primates. The examiner agrees that the applicants have provided evidence for the promotion of an immune response in mice. The examiner, in holding with the

prior art, disagree that the demonstration of eliciting an immune response in a mouse is predictive of success in primates.

Claim Rejections - 35 USC § 102

New grounds of rejection.

Claims 2, 3, 4, 6 and 8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Houghton et al US Patent 5,371,017

Applicants have amended the claims such that the broadest claim encompassing any recombinant nucleic acid encoding HCV structural proteins has been cancelled (Claim 1.) Further, the applicants have changed the dependency of rejected claims such that the essential elements of the invention have been more narrowly defined. Claims 2, 3, 4 and 8 have been amended to depend from claim 6. Claims 2, 3, 4 and 8 are drawn to nucleic acids encoding HCV proteins NS3, NS4 and/or NS5. Claim 3 specifies that the nucleic acid encode a fusion protein comprising the NS proteins. Claim 4 specifies a minimum fragment size of 50 amino acids. The independent claim, claim 6, recites that the HCV NS protein encoding nucleic acid further consists of a promoter, enhancer, polyadenylation sequence and optionally the HCV 5'UTR. Lastly, claim 8 is drawn to a recombinant cell comprising the nucleic acid of claim 6.

Houghton et al recite an isolated polynucleotide encoding HCV protease (see Claims beginning at column 85.) HCV protease is NS3. Houghton et al further disclose that the polynucleotide comprising NS3 is intended for expression in eukaryotic and

prokaryotic cells. (See column 7 line 50 to column 9, line 45). They note that "Suitable promoters are also known in the art ...Mammalian cells may also require a terminator and poly-A addition sequences. Enhancer sequences which increase expression may also be included..." Hence , the disclosure of Houghton et al clearly anticipate Claims 2, 4, 6 and 8. Houghton et al claim "A composition comprising a polynucleotide which encodes a fusion protein comprising Hepatitis C virus (HCV); and a fusion partner" (column 85, claim 3.) Claim 3 of the instant application is, therefore, also anticipated by Houghton et al.

Claim Rejections - 35 USC § 103

Claims 9-13 were previously rejected as being obvious over the teaching of Selby et al in view of Selden. Applicants have cancelled claim 9 and amended claims 10-13 to further define the scope of the claims such that the pharmaceutical compositions of each claim encompass nucleic acids which comprise a promoter, enhancer and polyadenylation sequence. These limitations were previously not included in claims 9-12. The examiner agrees with applicants in that the Selby reference does not teach all of the elements set forth in claim 13. Further, in view of the added limitations incorporated into the independent claims, the examiner agrees with the applicant that the Selby reference has been obviated in regards to amended claims 10-13.

New Grounds of Rejection

Claim 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent NO 5,371,017 as applied to claims 2, 3, 4, 6 and 8 above, and further in view of Selden et al.

As outlined above, Patent 5,371,017 discloses the limitations of a promoter, enhancer and polyadenylation signal. Patent 5,371,017 does not specifically recite the re-suspension of nucleic acids in solutions deemed suitable by the Inventors of the instant application for use in pharmaceutical compositions. The Examiner, in reiterating the position of the previous Office Action holds that the re-suspension of nucleic acids in solutions encompassed by the scope of the term pharmaceutical composition are regularly performed by individuals skilled in the art.

Selden et al, as noted in the previous Office Action, disclose the use of tris-buffered saline for the re-suspension of nucleic acids. The Examiner further points to the disclosure of the applicants regarding possible pharmaceutical carriers: "In some cases isotonic solutions such as tris buffered saline is used." (pg 13 lines 29 and 31) .

One of ordinary skill in the art would have been motivated to resuspend nucleic acids in a pharmaceutically acceptable buffer because nucleic acids can be easily dissolved in isotonic solution, TBS or water, and this is routine practice in the art. Therefore, the invention as a whole would have been prima facie obvious to one of skill in the art at the time the application was filed.

New Grounds of Rejection

Claim 6 – 8. 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent NO 5,371,017 and Selden as applied to claims 10-13 above.

Claims 7, 8 and 14 were rejected in the previous Office Action as being obvious over Selby et al and further in view of the state of the prior art. Claim 8, reciting a recombinant cell, has been amended to depend from claim 6. Claim 14 has been amended to depend from claim 13. Claims 6 and 13, as amended, specify the limitations that the nucleic acid incorporates a promoter, enhancer and polyadenylation sequence. These limitations were previously absent from claims 8 and 14. The amended claims

Claim 7 encompasses the limitations of Claim 6 and contains further limitations drawn to a nucleic acid encoding NS3, NS4 and/or NS5 wherein said nucleic acid comprises the Rous sarcoma virus enhancer and the cytomegalovirus promoter. Claim 8 includes the limitations of Claim 6 and is drawn to a recombinant cell comprising a NS3, NS4 and/or NS5 encoding nucleic acid , said nucleic acid also incorporating the Rous sarcoma virus enhancer and the cytomegalovirus promoter. Claim 14 encompasses the limitations of Claim 13 and is further drawn to a pharmaceutical composition comprising the nucleic acid specified in Claim 13 wherein the nucleic acid comprises the Rous sarcoma virus enhancer and the cytomegalovirus promoter.

The examiner maintains that the use of various promoter-enhancer combinations are well known in the art for use as expression vectors or for intended DNA vaccine

uses. By way of exemplifying the prior state of the art, Houghton et al (U.S. Pat 5, 371,017) explicitly states: "Suitable promoters for mammalian cells are ... known in the art and include viral promoters...Enhancer sequences which increase expression may also be included."(see col 9 lines 11-16) Houghton et al's disclosure point to the fact that the use of various promoters and enhancers are obvious to one of skill in the art. The specific combination of the instant application is not novel considering that it was commercially purchased and specifically meant for gene expression. The non-structural proteins of HCV were also well known in the art. Many different viral genes could have been used in the vector with a reasonable likelihood of success. Motivation for using a commercially available and tested vector in conjunction with a well known viral protein encoding nucleic acid can be found in the fact that it is a generally art excepted goal to characterize and express viral proteins.

Regarding the recombinant cell of Claim 8 comprising the recombinant nucleic acid molecule of Claim 6, Houghton et al disclose the use of mammalian cells in combination with non-structural protein containing vectors also comprising promoters and enhancers well known in the art. (see col 9, lines 6-18)

Conclusion

Claims 2-4, 6-8, 10-28, 32 and 33 are currently pending. No pending claim as originally filed or amended is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Drabik whose telephone number is 703-605-1156. The examiner can normally be reached on Monday-Friday from 9am to 5pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on 703- 305-4051. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Inquiries of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234. Questions regarding review of formality issues may be directed to Kim Davis, the patent analyst assisting in this application. She may be reached at 703-305-3015.

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